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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007	2448

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- Th MAILING DATE of this communication appears on th cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *30-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-61 are pending. Claims 1-29 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7 and 9-29, in Paper No. 14 is acknowledged. The traversal is on the ground(s) that to search the subject matter of all the groups would not be a serious burden on the Examiner and refer the Examiner to MPEP §803 [see p. 2 of the Response].

This is not found fully persuasive because the basis of the restriction requirement is not solely upon search burden. Indeed, MPEP §803 states that the criteria for restriction between patentably distinct inventions requires that

(A) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(i)); and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a) - § 806.04(i), § 808.01(a), and § 808.02).

After further consideration, the Examiner agrees to rejoin Groups I and II. The Examiner has provided reasoning as to why the inventions are independent in the prior Office action, and that the inventions recited have acquired a separate status in the art as a separate subject for inventive effort and require independent searches. The search for each of the inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the

invention of one group would not necessarily anticipate or even make obvious another group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 30-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

Drawings

The drawings filed on 6/8/01 are approved by the Draftsman.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written, is incomplete. The claim is directed to a method for the production of an antibody by an avian cell. However, the claim is missing critical steps. For example, the vector would have to be expressed before an polypeptide could be produced by the cell. Claims 2-29 depend from claim 1.

Claim 4, as written, is vague. The claim recites that the peptide region is "suitable" for isolation. It is unclear what the metes and bounds of the term "suitable" are. "Suitable" implies a latent property and the conditions for the latent property must be clearly defined. Therefore, it is unclear if the latent property is ever obtained.

Claim 5, as written, is unclear. The claim recites that the cell is "derived from" a chicken, etc. The term "derived from" is unclear because the metes and bounds of the term are not clearly defined. For example, how are cells that are "derived" from original cells different from those cells they were derived from?

Claim 9, as written, is unclear. The claim recites "a combination thereof" in line 3 of the claim. This is unclear because the metes and bounds of the term "combination" are not clearly defined. For example, is the "combination," portions of one particular vector (*e.g.,* a viral vector and a plasmid vector), or utilizing two separate vectors? Claims 10 and 11 depend from claim 9.

Claim 15, as written, is vague. The claim recites the term "operable", however, the metes and bounds of this term are not clearly defined. Operable is a latent term, simply because a promoter is operable in a cell does not mean that it is operating in the cells. Claim 16 depends from claim 15.

Claim 29, as written, is incomplete. The claim recites the components of an expression vector and states, "thereby forming a single-chain antibody" in the last

line of the claim. The claim is incomplete because the vector would have to be expressed for the single-chain antibody to be produced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 5, 9, 19-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Mohammed *et al.* [**Immunotechnology**, 1998, 4:115-125].

The claims are directed to methods for the production of an antibody by an avian cell comprising culturing the avian cell transfected with at least one expression vector comprising a transcription unit having a nucleotide sequence encoding an immunoglobulin polypeptide operably linked to a transcription promoter and a transcription terminator, wherein the cultured avian cell produces an immunoglobulin polypeptide capable of forming an antibody.

Mohammed teach expression of recombinant human antibodies in stably transfected DT40 cell lines. In particular, Mohammed teach that two types of

vectors were developed, one with the heavy chain of the immunoglobulin which resuls in the expression of a murine anti-dansyl variable region joined to the appropriate human heavy chain constant region. The other vector encodes the light chain which results in the expression of a corresponding murine anti-dansyl variable region joined to a human kappa light chain constant region. [See pp. 116-117, bridging ¶]. Mohammed teach that these two vectors were co-transfected with each of the vectors into a chicken B lymphoblastoid cell line, DT40 [see p. 117, section 2.2.]. The transfected cells were maintained in culture media for two days, wherein surviving colonies were screened by ELISA to verify expression of the chimeric antibodies.

Accordingly, Mohammed teaches the claimed invention.

Claims 1, 2, 4-9, 11, 12, 14-17, 20-29 b are rejected under 35 U.S.C. 102(e) as being anticipated by Ditullio *et al.* [WO 00/75300 A2, published June 2, 2000].

Ditullio teach methods of generating transgenic avian. In particular, they teach the introduction of a nucleic acid molecule into the genome of an avian aspecies by contacting *in vivo* a blastodermal cell of a fertilized hard shelled egg [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-

28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Ditullio that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10]. In particular, the cells of the blastoderm can be accessed by cutting or drilling a small hole in the eggshell and directly infusing the DNA into the blastoderm [see p. 7].

Accordingly, Ditullio anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 10, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* [WO 00/75300 A2, published June 2, 2000, cited above] when taken with Michael *et al.* [U.S. Pat. No. 6,143,559, published November 7, 2000].

The claims are directed to methods for producing an antibody by an avian cell comprising culturing the avian cell transfected with at least one expression vector comprising a transcription unit having a nucleotide sequence encoding an immunoglobulin polypeptide operably linked to a transcription promoter and a transcription terminator, and wherein the cultured avian cell produces an immunoglobulin polypeptide capable of forming an antibody. In further embodiments, the expression vector further encodes a second immunoglobulin polypeptide and an internal ribosome entry site [IRES] [claim 3], wherein the expression vector is a viral vector selected from the group consisting of avian leucosis virus, adenoviral vectors, transferrin-polylysine enhanced adenoviral vectors, human immunodeficiency virus vectors, lentiviral vectors, Moloney murine leukemia virus-derived vectors or variants thereof [claim 10]; and in further embodiments, the transcriptional promoter is a cytomegaloviral promoter [claim 13].

Ditullio teach the introduction of a nucleic acid molecule into the genome of an avian species by contacting *in vivo* a blastodermal cell of a fertilized hard shelled egg [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-

12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Ditullio that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10].

Ditullio differ from the claimed invention in that they do not teach or suggest the expression vector further encodes a second immunoglobulin polypeptide and an internal ribosome entry site [IRES], that the vector is a viral vector, and that the promoter is the cytomegaloviral promoter. However, prior to the time the claimed invention was made, Michael teach methods of producing monoclonal antibodies in an avian system, and in particular, chickens. Michael teach that the human

cytomegalovirus immediate early gene promoter is a promoter that can be used to obtain high-level of expression of a coding sequence of interest, and that by employing such a well-known promoter, the level and pattern of expression can be optimized [col. 16, lines 47-63]. Michael further teach that the use of IRES elements can create multigene, or polycistronic messages. They teach that IRES elements can be linked to heterologous open reading frames, and that by virtue of the IRES element, multiple genes can be efficiently expressed by a single promoter or enhancer to transcribe a single message [col. 19, lines 5-21]. Michael teach that genetic constructs can be introduced into cells by both viral and non-viral transduction. Viral methods include adenoviral, and adeno-associated viral vectors [col. 19, lines 30-45].

Accordingly, in view of the combined teachings of Michael and Ditullio, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the methods of generating antibodies from avian cells, as taught by Ditullio, by use of the cytomegaloviral promoter, an IRES element, or by use of a viral vector, as taught by Michael, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, as supported by Michael, that the cytomegaloviral promoter is a well-known and well-characterized promoter that would allow for optimal levels and patterns of gene expression, that utilizing an IRES element

would facilitate expression of multiple genes, and that viral transduction is an efficient way to deliver a construct to a cell.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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